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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,834	09/08/2003	Rene Gantier	17109-012001 / 922	7681

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EXAMINER	
STOICA, ELLY GERALD	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/658,834	GANTIER ET AL.	
	Examiner	Art Unit	
	Elly-Gerald Stoica	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *8,9,46-74,140,142-144,279 and 306* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-7,16-19,21-23,40,43,44,139,141,307,308,315,316 and 332-345* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,5-9,16-19, 21-23,40,43,44,46--74,137-144,279,306-308, 315-316,332-345.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :01/09/2004, 01/14/2004, 11/09/2004, 01/04/2005,01/20/2005,08/31/2005,01/04/2006, 07/12/2006, 09/26/2006, 10/20/2006.

DETAILED ACTION

1. The preliminary amendments of 04/08/2004, 04/29/04 have been made of record, in addition to the 07/11/2005 and 08/19/2005.

2. Applicant's election with traverse of Group I, and of the species E by Q at position 41 in Seq. Id. No: 1 in the reply filed on 10/20/2006 is acknowledged. The traversal is on the ground(s) that the restricted groups contained overlapping subject matter and the requirement to elect a sequence and a species are mutually exclusive. This is not found persuasive because the restriction requirement is a prospective requirement and a fully comprehensive search of the all the claims would have constituted a considerable undue burden for the Examiner. Claim 1, 43 and 46 are not linking claims but they are genus claims. If a genus claim is found allowable the Applicant is entitled to a rejoinder. Therefore, the requirement is proper, predicated on the non-allowability of the genus claim. Regarding the election of species, the Applicant was requested to elect a single ultimate species for which the examination would be executed and in this view the election between a sequence and a species are not mutually exclusive. Modifications in the Interferon genus of proteins are not novel and each substitution needs to be thoroughly searched, thus constituting, again, an undue burden for the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Status of the claims

3. In view of the amendments filed by the Applicant on 10/20/2006 and on 12/01/2006, the claims 2-4, 10-15, 20, 24-39, 41-42, 45, 75-138, 145-278, 280-305, 309-314, and 317-331 have been canceled by the Applicant. By electing the species E41Q for the Seq. Id. No: 1, the Applicant elected to prosecute an interferon alpha cytokine 2b. Therefore, the claims 8, 9, 46-74, 140, 142-144, 279, and 306 are drawn to non-elected species and therefore are withdrawn by the Examiner.

The claims 1, 5-7, 16-19, 21-23, 40, 43, 44, 139, 141, 307, 308, 315, 316, 332-345 are examined.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 1,5, 6, 16, 18, 19, 21-22, 43, 44, 307, 308, 315-316, and 332-339 rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Testa et al. teaches of mixture of natural human alpha interferon species and subunits, known as IFN-αn3a, obtained from human blood upon induction with a virus (Example 1 and 2). Therefore, they are considered to be produced naturally and thus constituting non-statutory subject matter. The specific components are presented in table 11 and the N- terminal and C terminal sequences are described in tables 10 and 12 respectively. The components of the mixture, designated by the peak # of the HPLC

purification process, contain peaks 2-6 that harbor IFN alpha 2b variants containing the mutation M16I, which, according to the claims and the specification of the instant application, confers the mutant increased resistance to proteolysis and all the biochemical and biological properties of the mutants claimed in the instant application. For instance, peak #3 (the first mutant has the M16I mutation) has an increased antiviral specific activity than peak #1.1 and 1.2 (which contain the IFN α -2b) (table 4 corresponding lines). Its specific antiviral activity, as measured by the RK-13 cells, is between 40-80 times higher than the corresponding activity for the peak # 1.1or 1.2, while its antiproliferative activity (measured in Daudi cells in the presence of the cytokine) is 1.6-2 times higher than the corresponding activity for the peak # 1.1or 1.2 (Table 4). The mutant of peak # 3 contains, in addition to the M16I mutation, at least two more mutations located in the N terminus (T14A and R22G). By the description provided in the patent, any of the components of the IFN- α n3a mixture is intrinsically a structurally homolog of I IFN-α 2b and containing the mutations M16I; meet the limitation of the instant claims. The mutant of peak #2 has an antiviral activity approximately 1.05 of the component of peak 1.1 or 1.2 while the antiproliferative activity is between 1.1-1.4 of that of the component of peak 1.1 or 1.2 and thus the limitations of claim 339 are met.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1,5, 6, 16-18, 19, 21-22, 40, 43, 44, 139,141, 307, 308, 315-316, and 332-340, and 343 are rejected under 35 U.S.C. 102(b) as being anticipated by Testa et al. (U.S. Pat. 5,676,942, 10/14/1997).

The claims are drawn to an mutant interferon alpha cytokine, comprising one or more amino acid replacements in its sequence of amino acids, whereby the interferon alpha cytokine exhibits increased resistance to proteolysis compared to the unmodified interferon alpha cytokine that does not comprise the one or more amino acid replacements (claim 1), wherein the unmodified interferon alpha cytokine is an interferon α-2b (IFN α -2b) (Seq. Id. No: 1) (claim 5). The mutant IFN α -2b interferon is selected from among proteins comprising one or more single amino acid replacements (claim 6). The mutant IFN α cytokine has an increased antiviral activity compared to the unmodified cytokine (claim 16) measured by replication by RT-per (claim 17) and has more the antiviral than antiproliferative activity when compared to the unmodified cytokine in the presence of the cytokine (claims 18-19). The IFN α -2b may comprise two or more mutations (claims 21-22) and may be part of a pharmaceutical composition (claim 40) which may be formulated for oral administration (claim 343). Claims 43 and 44 are drawn to the mutant of claim 1 that is a structural homolog of IFN α -2b. Claims 139 and 141 is drawn to an mutant interferon α-2b (IFN α -2b) having increased stability or increased activity, compared to the unmodified cytokine, assessed by measuring the antiviral or antiproliferation activity after incubation with either mixtures of proteases,

individual proteases, blood lysate or serum. Claims 307 and 308 are reiterations of claim 6. The mutant IFN α -2b of claim 308 has more antiviral activity compared to the unmodified cytokine (claim 315 and 316). The interferon alpha cytokine of specified in claim 1 exhibits increased stability, in vivo and in vitro and exhibits increased or comparable antiviral or anti-proliferative activity compared to the compared to the unmodified cytokine (claims 332-340).

The teachings of Testa et al. were presented supra. By the nature of obtaining the mixture of their invention, the mixture would have been exposed to serum or blood lysate. The method of assessing the antiviral activity as in claim 17 of the application does not affect the properties of the mutant cytokine and therefore is not given patentable weight. Testa et al. also teach about the composition of his invention as a pharmaceutical composition (claim 1 of the patent) and possible formulated for oral administration (Col. 9, lines 24-35).

Therefore all the conditions and limitations of the claims 1,5, 6, 16, 18, 19, 21-22, 40, 43, 44, 307, 308, 315-316, and 332-339 were anticipated by Testa et al.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 7, 23, 341, 342, 344, and 345 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heinrichs et al. (WO 01/25438, 04/12/2001-cited by the Applicant) in view of Blank et al. (Eur. J. Biochem., 265, 11-19, 1999)

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 7 is drawn to a human mutant interferon α-2b comprising the E41Q amino acid replacement in its sequence of amino acids, whereby the mutant exhibits increased resistance to proteolysis compared to the unmodified interferon alpha cytokine that does not comprise the one or more amino acid replacements. Claim 23 is drawn to a human mutant interferon α-2b comprising the E41Q amino acid replacement in its sequence of amino acids (that is Seq. Id. No: 87), whereby the mutant exhibits increased resistance to proteolysis and further comprises the mutation R23K (claim 23). Claims 341-342 and 343-344 are drawn to mutants corresponding essentially to the Seq. Id. No: 87.

Heinrichs et al teach novel interferon-alpha homologue polypeptides. The mutants of the invention posses clinical utility in that they are designed towards optimization for use as pharmaceuticals and to overcome dose-limiting toxicity, receptor cross-reactivity, and short serum half-lives significantly reduce the clinical utility of many of these cytokines The existence of abundant naturally occurring sequence diversity

within the interferon-alphas (and hence a large sequence space of recombinants) along with the intricacy of interferon-alpha/receptor interactions and variety of therapeutic and prophylactic activities creates an opportunity for the construction of superior interferon homologues (p. 2-3). Heinrichs et al. do not specifically teach the mutation E41Q or the R23K. Blank et al. teach possible cleavage sites for the IFN α-2b molecule (Fig. 5), which include the E41 residue, region cleavable by Glu-C protease. The R23K mutation is found naturally in IFN α-2a as indicated in Seq. Id. No:182.

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to use the methods of Heinrichs to mutate the interferon α-2b at E41 to confer the mutant increased resistance to Glu-C protease with a reasonable expectation of success. The motivation to do so would have been suggested by Heinrichs et al namely to improve the serum half-life and stability.

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elly-Gerald Stoica whose telephone number is (571) 272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER